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**DUAL TASK PERFORMANCE
AND
ANTIHISTAMINE USE**

by

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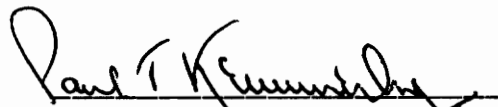
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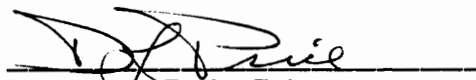
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DUAL TASK PERFORMANCE
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(ABSTRACT)

Research has shown that many antihistamines produce sedative effects as well as impair psychomotor performance. Performance testing of antihistamines, however, has not produced reliable evidence that there are behavioral effects at therapeutic dose levels. Therefore, the objective of this research was to determine whether a complex cognitive and motor task (memory search and tracking combination) showed a performance deterioration under the influence of two antihistamines (benadryl and hismanal) and to determine if the chosen task was of sufficient sensitivity to register decrements in performance at therapeutic dose levels of either of these two antihistamines.

Thirty male subjects were divided into five groups of six subjects each. Each of the five groups was tested one day per week for three consecutive weeks. All subjects received all three treatments (two antihistamines and a placebo) over the course of the test sessions. Order effect of the drug administration was counterbalanced.

Analyses of variance showed that benadryl impaired performance on both components of the task as expected. Performance under hismanal did not vary significantly from the placebo.

Post hoc testing further revealed an expected significant effect of benadryl three hours following ingestion for three out of four dependent variables. Again, hismanal effects did not vary significantly from those of the placebo.

Hence, the memory/tracking combination task registered an expected performance impairment by benadryl which implies sufficient sensitivity of the task to register decrements. Also, hismanal displayed an expected lower incidence of behavioral effects as measured by response time and tracking error, which implies hismanal's usefulness in facilitating normal performance.

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TABLE OF CONTENTS

INTRODUCTION	1
Problem Statement.	1
LITERATURE REVIEW.	5
Histamine/Antihistamine.	5
Pharmokinetics.	6
Hismanal (astemizole)	6
Benadryl (diphenhydramine).	9
Antihistamine Use and Psychomotor Performance.	12
Visual	13
Visual-motor	13
Cognitive.	16
Driving.	18
Antihistamine Use and Sedation.	19
Antihistamine Use and Dual Task Performance.	20
Cognitive Tests.	22
METHOD.	23
Subjects.	23
Experimental Design.	24
Task Description.	28
Dependent Measures.	30
Equipment.	30
Procedure.	31

RESULTS.....	36
DISCUSSION AND CONCLUSIONS.....	62
REFERENCES.....	67
APPENDIX.....	74
VITA.....	85

LIST OF TABLES

<u>Title</u>	<u>page</u>
1. Effects of H1 Antagonists on Psychomotor Performance.	3
2. Incidence (%) of Adverse Effects.	8
3. Summary of Adverse Reactions.	10
4. Effects of H1 Antagonists on Psychomotor Performance.	14
5. Correct Responses in Dynamic Visual Acuity Task.	15
6. Personal Data of Subjects.	25
7. Analysis of Variance Table Summary Table for Mean Response Time to Incorrect Probe.	39
8. Newman-Keuls Comparisons for Session Effect for Mean Response Time to Incorrect Probe.	42
9. Newman-Keuls Comparisons for Drug Effect for Mean Response Time to the Incorrect Probe.	43
10. Analysis of Variance Summary Table for Mean Response Time to the Correct Probe.	44
11. Newman-Keuls Comparisons for Session Effect for Mean Response Time to the Correct Probe.	46
12. Simple-Effect F-tests for Sessions Across Drugs for Mean Response Time to Correct Probe.	48
13. Newman-Keuls Comparisons for Session 2 Drugs for Mean Response Time to Correct Probe.	49

14.	Analysis of Variance Summary Table for Mean Response Time to Both Probes.	50
15.	Newman-Keuls Comparisons for Session Effect for Mean Response Time to Both Probes.	52
16.	Simple-Effect F-tests for Sessions Across Drugs for Mean Response Time to Both Probes.	53
17.	Newman-Keuls Comparisons for Session 2 Drugs for Mean Response Time to Both Probes.	54
18.	Analysis of Variance Summary Table for the RMS Tracking Error.	55
19.	Newman-Keuls Comparisons for Session Effect of the RMS Tracking Error	58
20.	Simple-Effect F-tests for Sessions Across Drugs for the RMS Tracking Error	59
21.	Newman-Keuls Comparisons for Session 1 Drugs for RMS Tracking Error.	60
22.	Newman-Keuls Comparisons for Session 2 Drugs for RMS Tracking Error.	61

LIST OF FIGURES

<u>Figure</u>	<u>page</u>
1. Counterbalance for treatment.	26
2. Group variable as a between subjects factor.	27
3. Test sessions scheduled for each test day.. . . .	29
4. Sessions effect for mean response time to incorrect probe.	40
5. Drug effect for mean response time to the incorrect probe.	41
6. Sessions effect for mean response time to correct probe and both correct and incorrect probes.	45
7. Session by drug interaction for mean response time to correct probe.	47
8. Session by drug interaction for mean response time to both probes.	51
9. Sessions effect for the RMS tracking error.	56
10. Session by drug interaction for the RMS tracking error.	57

INTRODUCTION

Problem Statement

Antihistamines work by preventing the effects of histamine produced by the body (United States Pharmacopeial Convention, 1985). Due to their lipid solubility, they cross the blood-brain barrier easily and affect the central nervous system causing sedation and deterioration of psychomotor functions (Unchern, Unchern, Chumsawat, Sriwatanakul, and Limsuwan, 1986). The occurrence of these effects has generated the precaution that antihistamines may impair the operation of heavy machinery, vehicle manipulation, and the performance of complex cognitive tasks. One reason that this impairment is only a precaution is due to the conflicting results of different experimental tasks. The World Health Organization (1983) stated that antihistamines are a main drug group which is dangerous for the road user and that the diversity of performance tests used in the investigation of antihistamines sometimes leads to difficulties in understanding what appear to be differing results. Also of interest is the possible effect of antihistamines on a pilot's judgment, vision or fine motor coordination, or tolerance to hypoxia (Whitehurst, 1980). Colds and hayfever which may require the use of antihistamines could possibly endanger the pilot's life by adversely affecting the pilot's performance which, in turn, could produce fatal consequences.

Whenever possible, we should work with medications that spare the cerebral cortex and facilitate normal defense mechanisms. It is of interest, therefore, to study the effects of newer antihistamines such as astemizole and terfenadine which are non-sedating and cross the blood-brain barrier with more difficulty than

the older antihistamines (Brandon, 1985; Fink and Irwin, 1979; Gengo and Gabos, 1987; Krstenansky and Cluxton, 1987; Nicholson, Smith, and Spencer, 1982; Nicholson and Stone, 1982; Sooknundun, Kacker, and Sundaram, 1987). Research indicates that both astemizole (hismanal) and terfenadine (seldane) have few, if any, sedative effects. The use of psychomotor performance tests has been more extensive for seldane than hismanal (see Table 1).

In addition, an assessment battery that is sensitive to therapeutic doses of antihistamines could be used to determine an individual's performance ability (Rice, 1990). The evaluation methods currently in use for antihistamine psychomotor research are not standardized. The development, administration, and scoring of tasks used in a study are often not reported and differ from one study to the next. Therefore, standardization of methodology in conjunction with a sensitive assessment battery is of utmost importance for comparison of research findings.

Hismanal was selected for performance testing as a result of the lack of studies on this particular antihistamine and its potential advantages over other antihistamines. These advantages include high and specific histamine H₁- antagonism, long duration of action, and absence of central sedative effects (Krstenansky and Cluxton, 1987; Vanden Bussche, 1984). Hismanal's median time to onset of action is 48 hours and the recommended adult dosage is 10 mg once daily. Maximum plasma concentrations occur one to four hours post ingestion (Richards, Brogden, Heel, Speight, and Avery, 1984). In addition, Heykants (1984) suggested that the half life of hismanal is one day, which is helpful if the daily dosage is forgotten.

Validation of a test system with drugs of known sedative potential is essential before assessment of new drugs is performed (Cohen, Posner, Ashsby, Smith, and Peck, 1984). For this reason, benadryl (diphenhydramine) was selected to serve as a control. This

TABLE 1

Effects of H1 Antagonists (Benadryl, Hismanal, and Seldane) on Psychomotor Performance (Rice, 1990)

	Benadryl (Diphenhydramine) (25-50)	Seldane (Terfenadine) (10)	Hismanal (Astemizole) (60)
Critical flicker fusion	50: -<18>	10: -<13>	(60-240)-<1,2,3>
Digit-symbol substitution test	50: +<5*> 75: -<6,7>	10-20: <4> 10: -<13>	60: <1,4,13,19> 120: -<19>
Arithmetic	25: +<16> 50: -<8> 75: -<7> 75: +<6>	10-20: -<4>	60: -<4,9,16>
Finger tapping	50: -<10>		
Reaction time	25: +<15> 25-100: -<11> 50: +<15,20**> 50: -<17> 100: -<2> 100: +<15>		60-240: -<2,3>
Tracking	25: +<15> 25-100: -<8,11> 50: +<14,15,17> 55-75: +<6,12> 100: +<15>	10-20: -<4>	60: -<1,3,4,14,19> 120: -<19>

*Significant effect for males only, **driving simulator

For each drug, the recommended therapeutic dose (mg PO) is indicated. Each entry shows the dose administered (mg PO), whether a significant effect was observed (+) or not (-), and the study from which the results were obtained. Referenced studies, by number, are: 1. Nicholson and Stone (1983); 2. Moser et al., (1978); 3. Luscombe et al., (1983); 4. Nicholson and Stone (1982); 5. Jaatela et al., (1971); 6. Baugh and Calvert (1977); 7. Baugh and Calvert (1976); 8. Hughes and Forney (1964); 9. Reinberg et al., (1978); 10. Carruthers et al., (1978); 11. Linnoila (1973); 12. Burns and Moskowitz (1980); 13. Nicholson, Smith, and Spencer (1982); 14. Moskowitz and Burns (1988); 15. Cohen et al., (1984); 16. Unchern et al., (1986); 17. Cohen et al., (1987); 18. Fink and Irwin (1979); 19. Nicholson and Stone (1986); 20. Gengo and Gabos (1987).
(An adaption of Table 1, White and Rumbold, 1988, p. 5)

drug has known central nervous system effects and provides assurance that any effect or lack of effect produced by the new drug (hismanal) is due to the action of that drug (Rice, 1990).

A person experiencing the symptoms of allergic rhinitis which may be perennial or seasonal (hayfever) may be reluctant to seek medical advice for fear of being taken off the job. A physician represents a threat to a pilot, for example, because he might discover a condition or prescribe a medication which could terminate the pilot's flying status. This threat is of grave importance to the pilot whose livelihood depends on his staying in the cockpit (Whitehurst, 1980). The same is true for truck drivers and assembly line workers whose jobs demand precise coordination and mental alertness. Therefore, instead of seeking medical attention, a person may choose to self medicate with over-the-counter medications. These over-the-counter drugs which are or contain antihistamines (benadryl or cold medications) may cause sedation and impair performance. It is for this reason that identification of a non-sedating antihistamine is needed.

LITERATURE REVIEW

Histamine/Antihistamine

Histamine is a physiologically active substance that binds to and stimulates histamine H1 and H2 receptors at several sites in the body (American Society of Hospital Pharmacists, ASHP, 1987). It also occurs naturally in the body. It is widely distributed in the tissues, organs, and body fluids of mammals (Bergersen, 1979; DiPalma, 1971). The release of histamine can be caused by allergens, various drugs, and tissue irritants, and may result in symptoms such as itchy skin, decrease in blood pressure, urticaria, edema of mucous membranes, peripheral circulatory failure, bronchospasm, and increased gastric acid secretion (DiPalma, 1971). Typical cardiovascular effects of histamine include direct and indirect microvascular dilation and increased vascular permeability (ASHP, 1987). In allergic conditions, histamine and other substances are secreted from mast cells, basophils, and other substances that stimulate antibodies. Histamine binds to and stimulates specific receptors in the nose, eyes, respiratory tract, and skin, causing typical allergy symptoms (ASHP, 1987).

The term antihistamine has been used to describe drugs that act as H1- receptor antagonists. Antihistamines work by blocking H1- receptor sites to prevent the action of histamine on the cell. They do not chemically inactivate, physiologically antagonize, or prevent the release of histamine (ASHP, 1987). Antihistamines are used in treatment of nasal allergies (seasonal and perennial allergic rhinitis), allergic dermatoses, allergic conjunctivitis caused by foods or inhaled allergens, urticaria, and motion sickness, just to name a few (ASHP, 1987).

Antihistamines are associated with a number of adverse effects. Most noted are central nervous system effects such as sedation, dizziness, and disturbed coordination. Some individuals experience restlessness, insomnia, tremors, euphoria, nervousness, delirium, palpitations, and even seizures (ASHP, 1987). Sedative effects may disappear after administration for two to three days. Adaptation to the sedative effects may in fact be a contributing factor to the reason why some individuals use them for their calming effect during the day and insomnia at night. As a result, they may end up taking the drug for the sedating effects rather than the antihistamine effects (Brandon, 1985). Brandon (1985) added that patients may state that their attention span seems to be improved and that they have less muscle tremor, tachycardia, and restlessness with medication in comparison to without medication. No specific research was cited by Brandon to support this statement.

Pharmacokinetics

Hismanal (astemizole). In 1985 seldane (terfenadine) was the first non-sedating antihistamine released in the U. S. (Carter, Wojciechowski, Hayes, Skoutakis, and Rickman, 1985, as cited by Krstenansky and Cluxton, 1987). Hismanal was the second one available and received F. D. A. approval in December, 1988 (W. Kravec, Janssen Research Foundation, personal communication with V. B. Rice, January 18, 1989). It is produced by Janssen Pharmaceutical. The recommended adult dosage is 10 mg once daily administered on an empty stomach (Krstenansky and Cluxton, 1987). With this dosage, peak plasma concentrations occur after one hour (Paton and Webster, 1985). Krstenansky and Cluxton (1987) stated that a meal reduces bioavailability by 60 percent and delays the time to peak concentration. Therefore, it is recommended that oral doses be taken one hour before or two hours after a meal.

Hismanal is approximately 96 percent protein bound and has rapid and extensive tissue distribution (Paton and Webster, 1985). As mentioned, it does not cross the blood-brain barrier easily and has a higher affinity for lung histamine-receptors than cerebellar histamine-receptors, which is one possible explanation for the lower incidence of central nervous system effects (Krstenansky and Cluxton, 1987).

Hismanal is extensively metabolized and is excreted primarily in the feces (Krstenansky and Cluxton, 1987). No unchanged hismanal appears in the feces and all metabolites are slowly eliminated (Meuldermans, Hendrickx, Lauwers, Hurkmans, Swysen, and Heykants, 1986, as cited by Krstenansky and Cluxton, 1987). Mean half-life ranges from 9.2 to 13 days with single doses and 18 to 20 days after two weeks to five months of usage (Krstenansky and Cluxton, 1987).

Hismanal has a delayed onset of action and is therefore not the antihistamine of choice for treatment of acute allergic symptoms. It is safe and effective in the treatment of seasonal allergic rhinitis, perennial allergic rhinitis, chronic urticaria, and allergic conjunctivitis. One limitation that it has is that it is not useful in treating nasal blockage and itching at the central part of the nasal cavity (Krstenansky and Cluxton, 1987). The major therapeutic use of hismanal is the treatment of outpatients with chronic or recurrent allergic conditions.

Hismanal side effects. The long half-life of astemizole has the disadvantages that a longer time is required to reach a steady concentration and that the drug cannot be eliminated quickly in the event of side effects (Moller and Johansson, 1984). It is for this reason that women of childbearing age should use it with caution. A list of reported side effects of hismanal and a placebo is summarized in Table 2. Adverse effects that occurred more

TABLE 2

Incidence (%) of Adverse Effects Reported in 744 Hismanal-treated and 331 Placebo-treated Patients (Vanden Bussche et al., 1984)

Adverse Effect	Hismanal	Placebo
CNS depression	14.7	13.3
CNS stimulation	0.7	1.2
Headache	4.8	6.0
Dry mouth	5.0	4.5
Nausea	2.2	2.4
Abdominal pain	0.5	1.5
Flatulence	0.5	0.0
Diarrhea	0.9	2.1
Rash	1.2	0.3
Eczema	0.4	1.2
Increased appetite	0.5	0.6
Increased weight	0.4	0.3

frequently (although not significantly) with hismanal than with the placebo include CNS depression, dry mouth, and increased weight. In another study by Bernstein and Bernstein (1986), hismanal and a placebo were compared and hismanal showed a greater frequency of occurrence for drowsiness, increased appetite/weight gain, and headache (see Table 3). Again, the hismanal effects were not significantly greater in frequency than placebo effects. These side effects, as in all medical research, are reported whether or not they are significant. In most studies the incidence of sedation for hismanal is lower than with older antihistamines (Krstensky and Cluxton, 1987).

Benadryl (diphenhydramine hydrochloride). Benadryl is marketed by Parke-Davis and is available in capsules, tablets, and liquid form. The usual adult dosage in capsule form is 25 to 50 mg administered three to four times daily at four to six hour intervals. Following oral administration of a single dose, the drug appears in plasma within 15 minutes and peak plasma concentration is attained within one to four hours (ASHP, 1988). The antihistamine effect appears to be maximal within one to three hours and may persist for up to seven hours. The sedative effect also appears maximal within one to three hours after administration and appears to be positively correlated with plasma drug concentration (ASHP, 1988).

Distribution of diphenhydramine into human body tissues and fluids has not been fully established, but the highest concentrations of the drug in rats occur in the lungs, spleen, and brain, with lower concentrations in the heart, muscle, and liver (ASHP, 1988). Diphenhydramine is 80 to 85 percent protein bound and is rapidly and almost completely metabolized. It is excreted in the urine and only about one percent of a single dose is excreted unchanged in urine (ASHP, 1987).

The following description and guidelines exist for benadryl

TABLE 3

Summary of Adverse Reactions During Both Double-Blind and Open Phases of Study (Bernstein and Bernstein, 1986)

Adverse Effect	No. of Adverse Episodes	
	Hismanal n = 38	Placebo n = 27
Drowsiness	2	0
Fatigue	1	1
Dryness of mucous membranes	1	0
Increased appetite/weight gain	5	0
Swelling of extremities	2	0
Nausea/vomiting	3	3
Headache	2	1
Bloating	1	0
Vertigo/dizziness	1	1
Nervousness	1	0
Rapid Breathing	0	1
Total	19	7

(ASHP, 1988).

Indications and Usage

1. antihistaminic: for allergic symptoms and conditions.
2. motion sickness: for active and prophylactic treatment of motion sickness.
3. antiparkinsonism: for adjunct treatment of parkinsonism.
4. nighttime sleep aid.

Contraindications

1. use in the newborn or premature infant.
2. use in nursing mothers.
3. hypersensitivity to diphenhydramine hydrochloride and other antihistamines of similar chemical structure.

Warnings:

Antihistamines should be used with considerable caution in patients/subjects with narrow-angle glaucoma, stenosing peptic ulcer, pyloroduodenal obstruction, symptomatic prostatic hypertrophy, or bladder-neck obstruction. In infants and children, especially, antihistamines in overdosage may cause hallucinations, convulsions, or death. As in adults, antihistamines may diminish mental alertness in children. In the young child, they may produce excitation. Antihistamines are more likely to cause dizziness, sedation, and hypotension in elderly patients.

Precautions:

1. General: Benadryl has an atropine-like action and should be used with caution in patients/subjects with a history of bronchial asthma, increased intraocular pressure, hyperthyroidism, cardiovascular disease, or hypertension.
2. Information for patients/subjects: Patients/subjects taking benadryl should be advised that this drug may cause drowsiness and has an additive effect with alcohol. They should be warned about engaging in activities requiring mental alertness such as driving a car or operating appliances, machinery, etc.
3. Drug interactions: Benadryl has additive effects with alcohol and other central nervous system depressants (hypnotics, sedatives, tranquilizers, etc.). Monoamine oxidase

inhibitors prolong and intensify the anticholinergic (drying) effects of antihistamines.

4. Carcinogenesis, impairment of fertility, mutagenesis: Long term studies in animals to determine mutagenic and carcinogenic potential have not been performed.

5. Pregnancy: Reproduction studies have been performed in rats and rabbits at doses up to 5 times the human dose and have revealed no harm to the fetus. There are, however, no adequate and well controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Adverse reactions:

1. General: urticaria (hives), rash, anaphalactic shock, photosensitivity, excessive perspiration, chills, dryness of mouth, nose, and throat.

2. Cardiovascular: hypotension, headache, palpitations, tachycardia, extrasystoles.

3. Hematologic: hemolytic anemia, thrombocytopenia, agranulocytosis.

4. Nervous system: sedation*, sleepiness*, dizziness*, disturbed coordination*, fatigue, confusion, restlessness, excitation, nervousness, tremor, irritability, insomnia, euphoria, paresthesia, blurred vision, diplopia, vertigo, tinnitus, acute labyrinthitis, neuritis, convulsions.

5. GI system: epigastric distress, anorexia, nausea, vomiting, diarrhea, constipation.

6. GU system: urinary frequency, difficult urination, urinary retention, early menses.

7. Respiratory system: thickening of bronchial secretions*, tightness of the chest and wheezing, nasal stuffiness.

*the most frequently reported side effects.

Antihistamine Use and Psychomotor Performance

Psychomotor performance testing of antihistamines falls into three categories: visual, visual-motor, and cognitive. Some

evaluations used frequently in the investigation of impaired performance are critical flicker fusion, digit symbol substitution, arithmetic, finger tapping, reaction time, and psychomotor tracking, as can be seen in Table 1 and Table 4.

Visual. Nicholson (1985), Nicholson, Smith, and Spencer (1982), and Nicholson and Stone (1986) all stated that dynamic visual acuity is impaired by antihistamine use. Triprolidine (10 mg in a sustained release form) was compared to both terfenadine (60 mg) and astemizole (10 mg) (see Table 5). Dynamic visual acuity is used to describe the ability of an individual to resolve detail of a moving target during ocular pursuit. It depends on the sensory and motor components of the ocular response and the feedback systems that link them (Nicholson et al., 1982). This study on triprolidine suggested that antihistamines slow both saccadic eye movement and smooth pursuit. Both of these ocular mechanisms could be involved in the performance of complex tasks. Pupil size was not altered by any of the three antihistamines. Nicholson and Stone (1986) examined the effects of triprolidine, terfenadine, and tazifylline on dynamic visual acuity. Triprolidine (10 mg) reduced the percentage of correct detections at the low target velocity at one hour ($p < 0.05$) and at the high velocity from one hour to six hours ($p < 0.05$). Trazifylline (15 mg) decreased the proportion of correct responses at the higher speed at two hours ($p < 0.01$). With terfenadine (60 and 120 mg) there were no performance decrements.

Visual-motor. Visual-motor skills have been evaluated primarily with tracking tasks, which have been reported to be oriented toward response execution in information processing terms (Perez, Masline, Ramsey, and Urban, 1987). Tracking tasks appear to be most sensitive to the disruptive effects of antihistamines (White and Rumbold, 1988).

Cohen et al. (1984) incorporated an adaptive tracking task into

TABLE 4

Effects of H1 Antagonists (triprolidine and clemastine) on Psychomotor Performance (Rice, 1990)

	Triprolidine (5)	Clemastine (1)
Critical flicker fusion	10: + < 1, 2, 10, 23 >	
Digit symbol substitution	1.25-5: + < 6 > 2.5: - < 7 > 5: + < 8 > 10: + < 1, 10, 23 > 10: - < 9, 2 >	1: - < 12 > 1-2: + < 6 >
Arithmetic	10-50: - < 9, 13 >	3: + < 14 >
Finger tapping	2.5: - < 7 > 2.5-5: + < 8, 15 >	3: + < 16 >
Reaction time	1.25-5: - < 6, 7 > 5: + < 8 >	1: - < 17 > 1-3: + < 6, 11 >
Tracking	2.5-10: + < 1, 9, 18 > 10: + < 10, 23 > 50: - < 13 > **	1: - < 19 > 1-3: + < 16, 20 >

**0.74 mg

For each drug, the recommended therapeutic dose (mg PO) is indicated. Each entry shows the dose administered (mg PO), whether a significant effect was observed (+) or not (-), and the study from which the results were obtained. Referenced studies are: 1. Nicholson and Stone (1983); 2. Nicholson, Smith, and Spencer (1982); 3. Hedges, Hills, Maclay, Newman-Taylor, and Turner (1971); 4. Levin, Barbat, Hedges, and Turner (1984); 5. Luscombe, Nicholls, and Parish (1983); 6. Peck, Fowle, and Bye (1975); 7. Hamilton, Bush, Bye, and Peck (1982); 8. Bye, Claridge, Peck, and Plowman (1977); 9. Nicholson and Stone (1982); 10. Nicholson and Stone (1984); 11. Jaatela, Mannisto, Paatero, and Tuomisto (1971); 12. Hindmarch (1976); 13. Hughes, and Forney (1964); 14. Reinberg, Levi, Guillet, Burke, and Nicolai (1978); 15. Bye, Dewsbury, and Peck (1974); 16. Levander, Hagermark, and Stahle (1985); 17. Hindmarch and Parrot (1978); 18. Nicholson (1979); 19. Seppala, Nuotto, and Koritila (1981); 20. Clark and Nicholson (1978); 21. Luscombe, Nicholls, and Spencer (1980); 22. Biehl (1979); 23. Nicholson and Stone (1986).

TABLE 5

Effects of Antihistamines on the Percentage of Correct Responses in Dynamic Visual Acuity Task at Four Target Velocities (Nicholson, Smith, and Spencer, 1982)

Drug	Target Velocity (deg/s)	Time (h) after Ingestion		
		1.0	2.5	4.0
Placebo	21	93.7	93.1	93.1
Terfenadine (60 mg)		94.4	92.4	92.7
Tripolidine (10 mg)		87.4*	80.7**	88.7
Astemizole (10 mg)		90.7	92.4	92.0
Placebo	43	80.6	80.7	82.0
Terfenadine		81.1	81.5	82.8
Tripolidine		65.8**	61.2***	74.2
Astemizole		82.4	74.7	79.5
Placebo	68	42.5	45.6	51.1
Terfenadine		40.3	48.2	48.7
Tripolidine		31.7	28.2**	36.8*
Astemizole		38.9	44.3	44.2
Placebo	83	13.8	17.4	21.7
Terfenadine		13.8	14.6	22.1
Tripolidine		11.7	10.0	10.7**
Astemizole		10.0	16.1	16.4

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

their study of diphenhydramine. The task required a subject to keep a spot inside a circle of 1.5 cm diameter which moved in a random manner over an oscilloscope screen. Performance was significantly impaired by all doses (25, 50, and 100 mg) of diphenhydramine. Cohen, Hamilton, and Peck (1987) used the same tracking task and also reported an impairment of performance with 50 mg of diphenhydramine.

Moskowitz and Burns (1988) performed a randomized, double-blind study to determine the effects of terfenadine (60 mg), diphenhydramine (50 mg), and a placebo on psychomotor performance. Visual search and recognition, critical tracking, divided attention, and vigilance tasks were evaluated. Diphenhydramine impaired subjects' performance one hour after ingestion. At three hours and five hours after ingestion, performance remained worse than with other treatments. Terfenadine did not impair subjects' performance as measured by the battery of laboratory tests.

Although tracking tasks are widely used to evaluate visual-motor performance, White and Rumbold (1988) stated that results of these tests are not clear. "Both positive and negative results have been obtained with the same drug, and the discrepancy cannot always be explained in terms of the dose used."

Cognitive. Information processing assumes that cognitive operations occur in stages. Each stage is dependent upon the previous stage. Wickens (1984) proposed the following stages: sensory processing, short-term sensory store, perceptual encoding, decision making, and response execution. Attentional resources feed the perception, working memory, decision, and response execution stages. Although this model is hypothetical, it provides utility in describing behavior of an actual system or process and can be used to generate testable hypotheses that are supported by the behavior

of the actual system or process (Sanders and McCormick, 1987). White and Rumbold (1988) provided a list of tasks that exercise different stages of the model:

1. The critical flicker fusion test requires a subject to state whether an intermittent light source appears to be flickering or steady. In terms of information processing, the test is said to measure the rate at which information is input. Some antihistamines have been found to lower the threshold (frequency at which the light appears flickering) while others have no effect.

2. Digit-symbol substitution requires a subject to view a code consisting of digit or letter symbol pairs and a list of symbols. Subjects must then substitute an appropriate digit (or letter) for as many symbols as possible in a given time period. This test measures the process of translation from perception to action and forms part of some intelligence tests. Impairment of performance following both low and high doses of triprolidine has been noted. However, some studies suggested no effect. Diphenhydramine and clemastine studies have reported similar discrepancies.

3. The focus of arithmetic tasks is also the translation from perception to action. These tasks might involve counting backwards from 1000 by sevens and performing simple arithmetic problems. Both diphenhydramine and clemastine have been found to significantly impair performance of these tasks.

4. Subjects doing finger tapping tasks are asked to tap their dominant-hand index finger on a plane surface as frequently as possible for a fixed time period. This task measures preparation and execution of the response. Performance has been noted to be impaired by a number of antihistamines, but findings have not always been consistent.

5. In a reaction time task the subject is required to make a motor response as quickly as possible to either an expected visual or auditory stimulus. Reaction time indicates the speed and efficiency of information processing. One variation is a choice reaction time task that involves two or more alternative stimuli with

corresponding alternative responses. A number of studies have indicated an increase in reaction time following antihistamine ingestion.

6. Finally, there is a large variety of tracking tasks. All of them require a subject to guide something moved by hand along a predetermined path. Some examples are guiding a stick through concentric circles, positioning a dot in the center of a moving circle on an oscilloscope, and moving a dot on an oscilloscope along a marked path. Tracking is said to measure sensori-motor integration which is the basis of most skilled behaviors. Results from tracking tasks have not been clear and there have been both positive and negative results.

Driving. Driving, whether in a simulator or on the road, involves visual, visual-motor, and cognitive skills. Gengos and Gabos (1987) found reaction time on a simulator to be increased following a 50 mg administration of diphenhydramine. Betts, Markham, Denenham, Mortiboy, and McKeivitt (1984) also found impairment of driving skills, but triprolidine (10 mg) and terfenadine (60 mg) were used instead of diphenhydramine. Triprolidine impaired driving performance whereas terfenadine did not. Also, they found that even though subjects were aware of their impairment, they were unable to prevent deterioration of their performance. As a result, physicians who prescribe antihistamines that are known to impair performance should advise patients to stop driving or to use an antihistamine that does not impair performance. Cohen et al. (1984) found that all doses of diphenhydramine (25, 50, and 100 mg) did not impair driving performance, but that all dose levels produced performance deterioration on adaptive tracking, body sway, and visual reaction time in a laboratory setting. Cohen et al. (1984) concluded that off-road driving tests do not provide a sensitive method of assessing sedative effects of drugs.

Antihistamine Use and Sedation

Antihistamines often cause drowsiness and impaired performance and these effects appear to be related (Nicholson and Stone, 1986). If this correlation is valid, it could follow that monotonous, boring tasks would be more sensitive to the effects of antihistamines than brief, interesting tasks. Vigilance tasks are often considered to be monotonous and boring. Moskowitz and Burns (1988) conducted a vigilance task which required a simple stimulus response. Significant effects were found with the use of diphenhydramine. Another cited vigilance task used a continuous performance task in which subjects were required to maintain depression of a resilient button (Fink and Irwin, 1979). Performance decrements were found with diphenhydramine use and would appear to be a result of sedative effects. They also reported that there was an increase in EEG slow wave activity with 25 mg and 50 mg doses of benadryl. Fink and Irwin (1979) concluded that there is a direct correlation between the degree of sedation and antihistaminic activity and that antihistamines directly affect brain functions.

There have been no studies on the effects of antihistamines on sleep (White and Rumbold, 1988). Significant increases in estimated sleep duration have been reported following diphenhydramine administration (Teutsch, Mahler, Brown, Forrest, James, and Brown, 1975) and hydroxyzine (Brown, Adams, Haegerstrom-Portnoy, Jones, and Flom, 1975). Also, Roehrs, Tietz, Zorick, and Roth (1984) reported that diphenhydramine decreased the latency to sleep onset, but at the same time it did not alter the total duration of sleep (White and Rumbold, 1988). In this same study, terfenadine did not differ from a placebo.

Antihistamine Use and Dual Task Performance

Both designers and operators of systems realize that performance is not all that is important in the design of a good system. It is just as important to take into account what demand a task imposes on the operator's limited resources (Wickens, 1984). In fact, a major concern between management and labor in the airline industry involves the concept of workload. The Airline Pilots Association argues that the workload required at peak times in the class of narrow-body air transports is excessive for a two-man crew on the flight deck (Wickens, 1984). As a result, the Federal Aviation Administration requires certification of aircraft in terms of workload criteria on recently designed systems (Wickens, 1984).

Combinations of a memory search task and a tracking task have been employed in research in order to test the assumptions underlying multiple resource models of attention (Perez et al., 1987). Research by Vidulich and Wickens (1981) employed just such a task combination. Results from this study indicate that the effect of visual input competition was borne mostly by the perceptual/cognitive memory search task, while the effect of manual output competition was observed in the response-loading tracking task.

The memory search-tracking task combination has not been used in studies involving antihistamines; however, dual task methodology has been employed in the study of the effects of chemical and environmental stressors on human performance (Perez et al., 1987). Studies by Putz and his associates (Putz, 1979; Putz-Anderson, Setzer, and Croxton, 1981; Putz, Johnson, and Setzer, 1977, as cited by Perez et al., 1987) have examined the effects of toxic substances on the performance of a tracking-tone detection task combination. This research found a significant effect of stressor (carbon monoxide and alcohol) on tracking performance but

not on the tone detection task (Perez et al., 1987).

Other research cited by Perez et al. (1987) involved the study of G-stress induced loss of consciousness on a two-dimensional compensatory task (Houghton, McBride, and Hannah, 1985). In this study, the above task was performed simultaneously with a choice reaction time task and a mental arithmetic task. The tracking task was primary and the others were secondary tasks. Results indicated: (1) significant impairment in the choice reaction time task and the mental arithmetic task, and (2) there was no impairment in the primary tracking task.

Moskowitz and Burns (1988) conducted a study on the effects of terfenadine (60 mg), diphenhydramine (50 mg), and placebo on skills performance. They employed a compensatory tracking task and visual search and recognition task combination. This combination was analogous to the information processing and response organization requirements of driving in a crowded urban area while processing a large amount of information generated by other cars, traffic signals, pedestrians, etc. (Moskowitz and Burns, 1988). Diphenhydramine impaired performance one hour post ingestion, and at three and five hours post ingestion, performance remained poorer than with other treatments. Subjective reports indicated feelings of sedation and slowing.

The above studies indicate that dual task methodology can be used in the evaluation of complex performance under an environmental stressor. The Systems Research Laboratory's Combined Memory Search-Tracking Task (CMSTT) is such a task. This task is designed to measure workload in an operational environment and is a good candidate because (1) the combination of the two tasks results in a test that taps a wide range of processing resources, (2) the test difficulty can be varied by increasing tracking and memory search difficulty, and (3) it can examine the

effect on a subject's ability to efficiently time share.

Cognitive Tests

The task specific to this thesis is a memory search-tracking combination. The purpose of this task is to evaluate dual task performance. The assumption is that time sharing of two tasks, considered of equal importance and performed simultaneously, requires an increased mental workload. An unstable tracking task is performed with the subject's left hand and responses to the Sternberg Memory Search Task are performed with the right hand. The focus of this task is on time sharing ability.

Research indicates that the memory search portion of this task is a perceptual/cognitive task and taps verbal skills, while the tracking portion is a response processing task and taps spatial skills (Perez et al., 1987).

As stated earlier, this research was conducted as an additional component to a larger research project. A combination of two test batteries, the Unified Tri-service Performance Assessment Battery (UTC-PAB) and the Complex Cognitive Assessment Battery (CCAB), were also used in this research. The cognitive tests of the CCAB that were used are following directions and route planning. The tests from the UTC-PAB included four-choice serial planning, code substitution, logical reasoning, mathematical processing, time wall, manikin, pattern comparison, interval production, and visual motor tracking. Both test batteries have been developed to measure the effects of pre-treatment drugs (medications which are used as counter-agents in chemical warfare) on the complex cognitive abilities required to perform critical U. S. Army tasks.

METHOD

Subjects

Thirty male subjects were recruited from the student body at Virginia Polytechnic Institute and State University. The 30 subjects were divided into five groups of six subjects. The use of only males eliminated the necessity for pregnancy screenings prior to each test session. Antihistamine studies often require females not to be using birth control pills and do not allow performance testing for several days prior to, during, and for several days following menstruation. Of the 30 recruited subjects, 29 subjects successfully completed all the required screening and testing.

The subjects were recruited with the use of advertisements posted throughout the campus of Virginia Polytechnic and State University. Potential subjects were initially screened with the use of a questionnaire presented over the telephone by a member of the research team. Subjects that passed the initial screening were required to meet with a member of the research team for an individual interview and to complete a medical questionnaire. The individual interview included an explanation of the experiment, exactly what would be required of the subjects, the amount of time required to complete the experiment, method of payment, and associated risks (see Appendix). Subjects were permitted to ask any questions. The medical questionnaire was developed in conjunction with Philip L. Barkley, M. D., Chief Medical Officer and Director of Health Services, Virginia Polytechnic Institute and State University. All questionnaires and the students' health records were reviewed by Dr. Barkley. Approximately 90 potential subjects filled

out medical questionnaires. The final 30 subjects were chosen on the basis of their medical history, availability for scheduled test days, and according to their date of response. Two weeks before the subjects began the experiment, subjects met with the members of the research team and were scheduled for their test days. This group interview/explanation included an introduction to the research team, an explanation of the experiment and its purpose, an emphasis on the time commitment for participation, and procedural requirements and constraints. The subjects read and signed the informed consent forms at this group meeting. The subjects used in this experiment possessed the characteristics in Table 6.

Experimental Design

To achieve the research objective a two-factor (3 treatments x 8 sessions) repeated measures, double-blind design focusing on subjects, sessions, and treatments was used. Double blind refers to the situation in which neither the investigators nor the subjects have knowledge of which condition the subject is receiving until all testing is completed. Each of the 30 subjects received all three treatments, one on each of three different days.

Order effect of the drug administration was counterbalanced, as shown in Figure 1. A balanced order design was achieved by assigning applicants, as they qualified, to the next available sequence number. A group order variable (five subjects per group) was employed as a between-subjects factor (Figure 2).

Although it was preferred for the same six subjects to return (as a group) on the three testing days, this was not necessary. Each subject was assigned a specific number which coincided with a medication packet number. The medication packet contained three sealed envelopes, labeled Test Day 1, Test Day 2, and Test Day 3 which indicated the order of administration for each subject.

TABLE 6

Personal Data of Subjects

	Mean	Standard Deviation	Range
Height	70.33	2.84	60-75 (inches)
Weight	160.31	20.70	125-220 (lbs.)
Age	23.54	4.18	20-36 (years)

	Test Days		
	<u>1</u>	<u>2</u>	<u>3</u>
Order 1	H	B	P
Order 2	B	P	H
Order 3	P	H	B
Order 4	H	P	B
Order 5	B	H	P
Order 6	P	B	H

Each order represents five randomly assigned subjects.

H = hismanal (astemizole)

B = benadryl (diphenhydramine)

P = placebo

Figure 1. Counterbalance for treatment (drug administration)

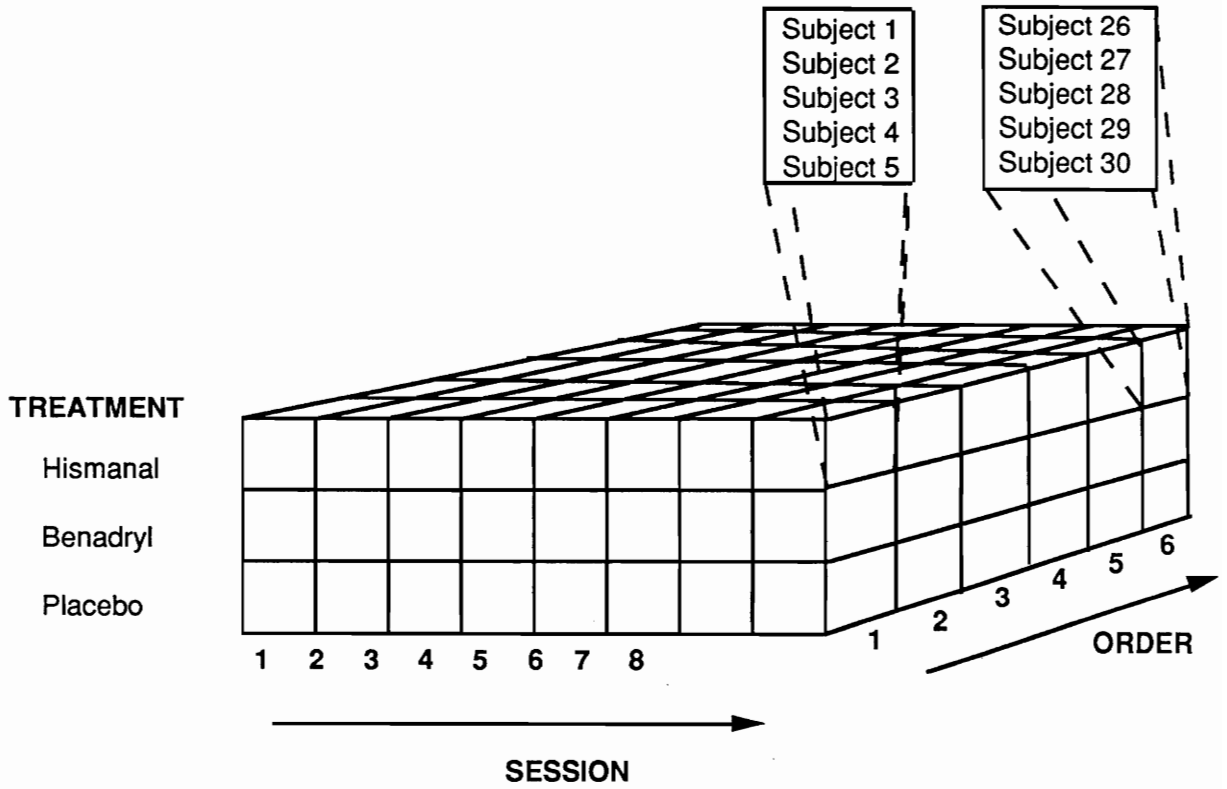


Figure 2. Group variable as a between-subjects factor.

On each treatment day, eight test sessions were scheduled for each subject (Figure 3). The order of the individual test measurements was controlled by giving the tests in the same order for each session.

Task Description

The Combined Memory Search-Tracking Task (CMSTT), designed to measure workload in an operational environment, is a performance assessment test generated by Systems Research Laboratories (SRL). It is intended to tap information processing resources dedicated to time sharing ability. Subjects were required to track with their right hand and respond with their left hand to the Sternberg memory search stimulus (probe). Total task time per session was 3 minutes, 48 seconds.

The Sternberg memory search involves the following: (1) subject is shown a set of letters or numbers to be remembered (positive set); (2) this display is erased; (3) a single probe is presented on screen every 8 seconds which is either a member of the positive set or not a member; and (4) subject responds by deciding whether or not the probe is a member of the positive set.

To start a trial, the subject was shown the positive set for the Sternberg task. The positive set contained eight randomly assigned letters to be remembered. This display was erased at the subject's control and the trial began two seconds later. Subjects were told to respond as quickly and as accurately as possible, and that both tasks were of equal importance. Either an incorrect probe (a letter that did not appear in the positive set) or a correct probe (a letter that did appear in the positive set) appeared on the screen. It was the task of the subject to decide whether the probe was incorrect or correct. Response was executed by pushing one of two color-coded buttons (one for an incorrect probe and one for a correct probe).

Hismanal	**	*	*	*	*	*	*	*	*
Benadryl	**	*	*	*	*	*	*	*	*
Placebo	**	*	*	*	*	*	*	*	*

Hours	7am	8	10	12	2pm	4	6	8	10
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* test session, ** drug administration

Figure 3. Test sessions scheduled for each test day.

At the same time the memory search task started, the compensatory tracking task began. This required the subject to maintain the dynamically displaced cursor over a stationary target area. The cursor's movements were limited to the horizontal plane (left and right movements only) and controlled by means of a joystick. The forcing function of the tracking task is complex but undefined by SRL. The tracking task ramped up in difficulty to a level that was not impossible to track but required constant attention in order to be controlled (SRL, 1987). The low force multiplier, or λ , was set at 1.0 and the high multiplier was set at 3.0. This multiplier takes the error off center of the cursor position and adds this amount to the position.

Dependent Measures

The study incorporated four different dependent variables:

1. Mean response time (in ms) to an incorrect probe,
2. Mean response time (in ms) to a correct probe,
3. Mean response time (in ms) to both of the probes, and
4. A root mean square (rms) tracking error. This value indicates the error in offset from the center of the target. Units are arbitrary, due to the inaccessibility of information regarding calculation of the rms value.

Equipment

The tests were computerized and designed to run on IBM-PC compatible micro-computers meeting the following minimal specifications:

1. CPU processor: a 16-bit 80286 processor with a clock speed of 8.0 Mhz.
2. Math coprocessor: 80287 math coprocessor.
3. Disk storage: two soft-sectored, double-sided,

- double-density, 48 tracks-per-inch 360 kilobyte 5.25-inch floppy disk drives and one 20 megabyte hard disk drive.
4. Random access memory: 640k RAM memory.
 5. Buss: must be IBM compatible, with 4 unused slots minimum.
 6. Input/Output: two RS-232C serial ports and one parallel port.
 7. MS-DOS operating system version 3.2 or above.

The video display specifications are as follows: a 12-inch high-resolution RGB color monitor that operates in a non-interlace mode, capable of a minimum of 640 x 400 pixel resolution, with a minimum of 16 colors.

The Systems Research Laboratory PC-Labpac Multifunction Board, designed specifically for UTC-PAB , combined the multi-event timer and workstation interface. It is a modular "plug-in" style unit which can contain three subject response apparatus simultaneously. Modular response apparatus required were a 180-degree switching joystick (used in the tracking and the tracking/memory search tasks) and a numeric keypad (also used in the aforementioned tasks).

Although not required, an uninterruptible power supply was utilized for each individual work station. This supply not only provided power to continue functioning in case of an outage, but more importantly it protected the equipment from a possible "head crash" in the event of an outage.

Procedure

Training. Subjects who were selected for this experiment were scheduled for 6 hours of training in either two 3-hour sessions

or one 6-hour session. Total training time ranged from five to nine hours. Two weeks were spent training all the subjects.

During the training sessions each subject was required to perform most of the tasks presented in the testing session to an asymptotic level ($\pm 5\%$ of his score and time for the previous two sessions). The tasks were divided into four main groups: (1) tracking, memory search, and tracking/memory search, (2) UTC-PAB, (3) CCAB, and (4) visual search. Groups 2, 3, and 4 were required for Valerie Rice's dissertation work and Gail Whitehouse's thesis work. These groups could be presented in any order depending upon time constraints, however, most subjects received the four groups in the order presented above. Written instructions, verbal explanation, time for subject questions, and a brief demonstration were given prior to the subject beginning his training for the tracking/memory search tasks. Instructions for all other tasks were presented to the subjects on the computer screen immediately before the corresponding tasks were to be performed. Prior to beginning training, subjects completed a personal information questionnaire which included self ratings in several areas.

Testing. For data collection, subjects were divided into five groups of six subjects each. Each of the five groups was tested one day per week for three consecutive weeks, for example, three Fridays in a row. The five different groups were tested on Tuesday, Thursday, Friday, Saturday, and Sunday.

Subjects were required to perform a baseline (review) session sometime the day before they were to be tested. This baseline session consisted of a brief review (a few repetitions of the tasks conducted on the computer) of all the tasks to be performed during the testing sessions. Also during the baseline session, which took approximately one hour to complete, subjects were given any final instructions or reminders that pertained to the next day's testing

sessions.

Subjects were given a wake-up call at 6:30 a.m., if they so requested, on the day they were tested. Subjects were required to be at the laboratory at 7:00 a.m. Subjects were instructed not to eat or drink anything before they arrived at the laboratory because the drug needed to be taken on an empty stomach. Subjects were permitted to eat a light breakfast 30 minutes after ingesting the drug at 7:00 a.m. and before the testing batteries began.

Each subject received all three treatments (hismanal, benadryl, and placebo) over the course of his three testing sessions. For each testing session, two subjects received hismanal, two received benadryl, and two received placebo. Seven days later on the second test day, the same six subjects were tested, but each received a different drug than he did on the first test day. The third test day occurred one week later, with each subject receiving the third of the three drugs (whichever drug he did not receive on the first and second test days). This schedule was followed for all five testing groups.

Test batteries were administered one hour post drug ingestion and every two hours thereafter, as shown in Figure 3, for a total of 16 hours. Subjects were tested at 8:00 a.m., 10:00 a.m., 12:00 p.m., 2:00 p.m., 4:00 p.m., 6:00 p.m., 8:00 p.m., and 10:00 p.m. Before each test battery the subjects' heart rate, blood pressure, and temperature were taken and recorded. The subjects were permitted to talk, read, study, sleep, watch movies, or watch television between testing batteries. Subjects were not permitted to leave the general vicinity of the laboratory. A member of the research team remained with the subjects throughout the entire day and a licensed physician was on call (via a beeper). A record of the activities of the subjects (e. g., sleeping) between test batteries was made so that if data appeared strange a clue might be found as to what

happened.

Subjects were required to remain in the laboratory for a total of 16 hours (even if they should decide to cease participation in the study). This was necessary due to the long half life of hismanal.

The subjects brought their own breakfast. The subjects were permitted breakfast after ingesting the drug and before the first testing battery began. The subjects ate lunch after they completed the 12:00 p.m. test battery, and they ate dinner after the 6:00 p.m. test battery. Subjects were permitted to bring their lunch and dinner at the beginning of the day and keep it in the provided refrigerator, or someone would bring them their meals. Also, a member of the research team took orders and went to area fast food restaurants for some of the subjects' meals.

For all test sessions the specific tasks were presented in the following order: UTC-PAB, visual search, CCAB, tracking task, and tracking/memory search task. On the third test day each subject was asked to complete a final questionnaire.

Doses of the drug were in the therapeutic range and administered by mouth. The placebo did not contain any active ingredients. The dosage for benadryl was 50 mg and for hismanal, 10 mg. Medications were in capsule form and all identical in appearance. All the medications were individually packaged for each subject by Janssen Pharmaceutical Company. Sixty envelopes were prepared, three for each subject. Each envelope was labeled by subject number and test day. The drug envelopes were kept in a locked vault within a locked room. Only medications required for that particular test day were removed. In the case of an emergency, a special code was provided which could be broken to determine which drug a subject had taken. One code was broken for one subject and he was subsequently dropped from the study. A master

list of the contents of each envelope was supplied to the research team after the experiment was completed.

Subjects were paid \$4.00 per hour for the time actually spent participating in the study. If the subject completed the entire experiment, he was paid \$5.00 per hour. No payment was made for time spent during the initial screening process. Payment was made in cash at the end of the last test day.

RESULTS

For each of the four dependent variables, statistical analyses were employed to test for any significant differences among the three drug types and the eight test sessions. An analysis of variance (ANOVA) was utilized to test for any mean response time and rms error value differences which could be attributed to the drug type, session, and any interaction between the two. A Student Newman-Keuls range test was performed as a post-hoc comparison for any effects found significant, and a simple-effect F-test was performed to evaluate significant interactions. Statistical significance was set at the 0.05 level.

The ANOVA used to test any differences among mean response times to the incorrect probe revealed two significant results (Table 7). The main effect of session produced significantly different mean response times to the incorrect probe across the eight sessions. Subjects exhibited an improvement over the day with a general decrease in response time (Figure 4). Session 2 yielded a significantly longer response time than did session 8 (Table 8).

The main effect of drug was also found to be significant for the mean response time to the incorrect probe. Subjects performed the best with hismanal, and the worst with benadryl, while there was no difference between hismanal and the placebo (Figure 5). The interaction of main effects (session x drug) proved to be nonsignificant.

The means of the response times for the different sessions and drug types as well as the results of the Newman-Keuls tests for each are presented in Table 8 and Table 9.

With respect to mean response time to the correct probe, a sessions effect was found but not a drug effect (Table 10). Again, there was a general decrease in response time as the day progressed (Figure 6). The Newman-Keuls test for sessions effect of the mean response time is shown in Table 11. Means for session 1, 2, and 4 are significantly larger than those for session 6 and 8.

An interaction was also found between session and drug effects (Figure 7). A simple-effect F-test performed on sessions across drugs produced a significant result only at session 2 (Table 12). A further post-hoc Newman-Keuls comparison for this significant result shows the response time with benadryl to be significantly greater than those for the hismanal and the placebo groups (Table 13).

The mean response time to both of the probes exhibited results similar to those yielded by the correct probe situation. A significant sessions effect was found but no drug effect was found (Table 14). An interaction effect was also found to be significant (Figure 8). As with the case of the correct probe, there was a general decrease in response time over sessions with session 2 exhibiting the slowest response time. The means for response times to both probes at each session as well as the Newman-Keuls test are presented in Table 15, which shows sessions 1 and 2 to have longer times than sessions 6 and 8.

In addition, a simple-effect F-test performed on the session x drug interaction revealed a significant effect only at session 2 (Table 16). A Newman-Keuls comparison among drugs shows the benadryl response time to be significantly longer than the hismanal and placebo times (Table 17).

The ANOVA utilized to test any differences among rms

tracking error means revealed a significant session effect and a significant interaction (Table 18). The session means revealed a general decrease over time (Figure 9) and the session x drug interaction is shown in Figure 10. The means of the rms tracking error and the results of the Newman-Keuls test for the session effect are presented in Table 19. The tracking error for sessions 1 and 4 is larger than for session 8.

A simple-effect F-test again revealed a significant effect at session 2 as well as an effect at session 1 (Table 20). Both Newman-Keuls comparisons indicate tracking error with benadryl to be significantly greater than for the hismanal and placebo groups (Table 21 and Table 22).

TABLE 7

Analysis of Variance Summary Table for Mean Response Time (in ms)
to Incorrect Probe

Source of Variation	df	MS	F	p
<u>Between Subjects</u>				
Subjects (Subj)	28	2863995.29		
<u>Within Subjects</u>				
Sessions	7	1314938.67	2.20	0.0358
Sessions x Subj	196	597604.91		
Drug	2	2912197.91	4.37	0.0172
Drug x Subj	56	665692.76		
Session x Drug	14	922330.20	1.51	0.1040
Session x Drug x Subj	392	610574.44		
Total	695	9887334.18		

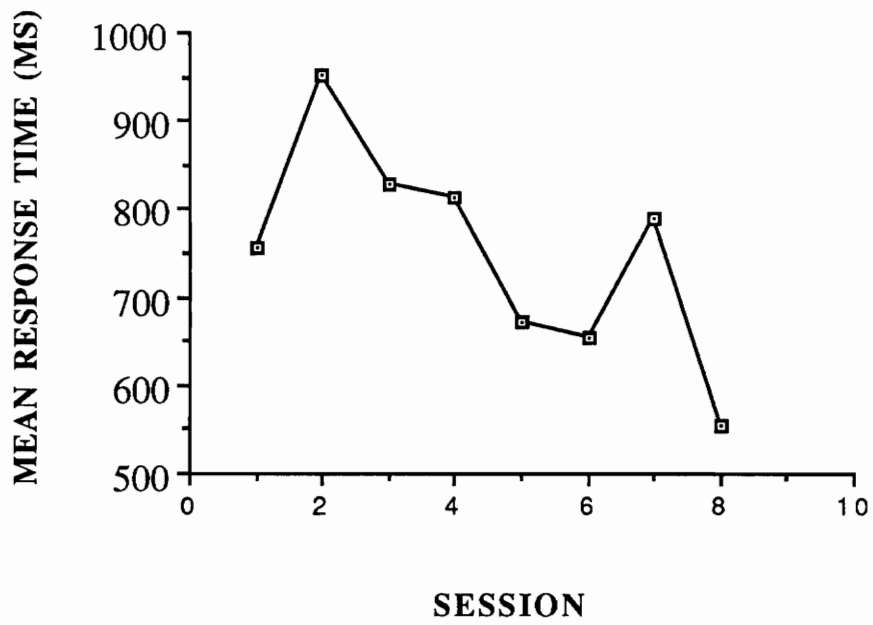


Figure 4. Sessions effect for mean response time to incorrect probe.

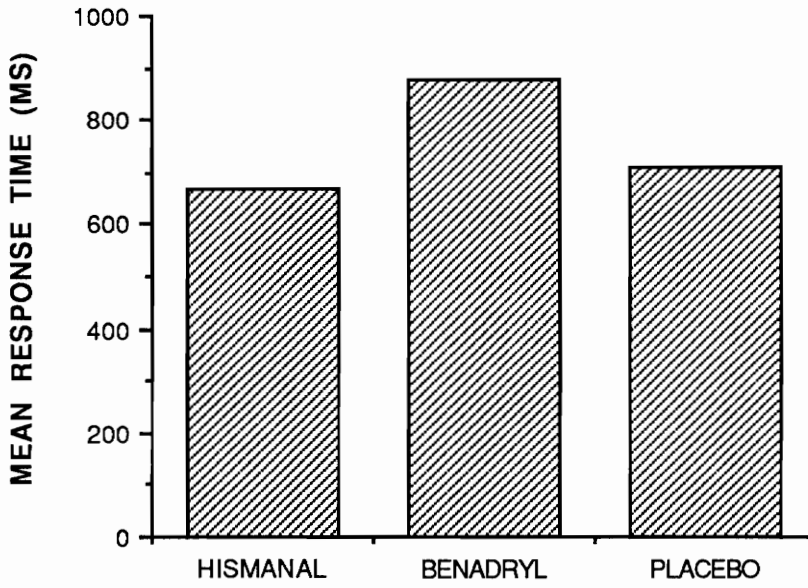


Figure 5. Drug effect for mean response time to the incorrect probe.

TABLE 8

Newman-Keuls Comparisons for Session Effect for Mean Response Time to the Incorrect Probe

Session	Time (ms)		
Session 2	950.6	A	
Session 3	827.3	A	B
Session 4	812.1	A	B
Session 7	790.0	A	B
Session 1	754.7	A	B
Session 5	672.7	A	B
Session 6	652.7	A	B
Session 8	553.3		B

Means with the same letter are not significantly different, $p > 0.05$

TABLE 9

Newman-Keuls Comparisons for Drug Effect for Mean Response Time to the Incorrect Probe

Drug	Time (ms)	
Benadryl	878.66	A
Placebo	709.63	B
Hismanal	666.75	B

Means with the same letter are not significantly different, $p > 0.05$.

TABLE 10

Analysis of Variance Summary Table for Mean Response Time (in ms)
to Correct Probe

Source of Variation	df	MS	F	p
<u>Between Subjects</u>				
Subjects (Subj)	28	1811611.78		
<u>Within Subjects</u>				
Sessions	7	178142.13	6.84	0.0001
Sessions x Subj	196	26053.79		
Drug	2	63380.84	0.64	0.5308
Drug x Subj	56	98955.14		
Session x Drug	14	43832.30	2.37	0.0035
Session x Drug x Subj	392	18466.26		
Total	695	101581.78		

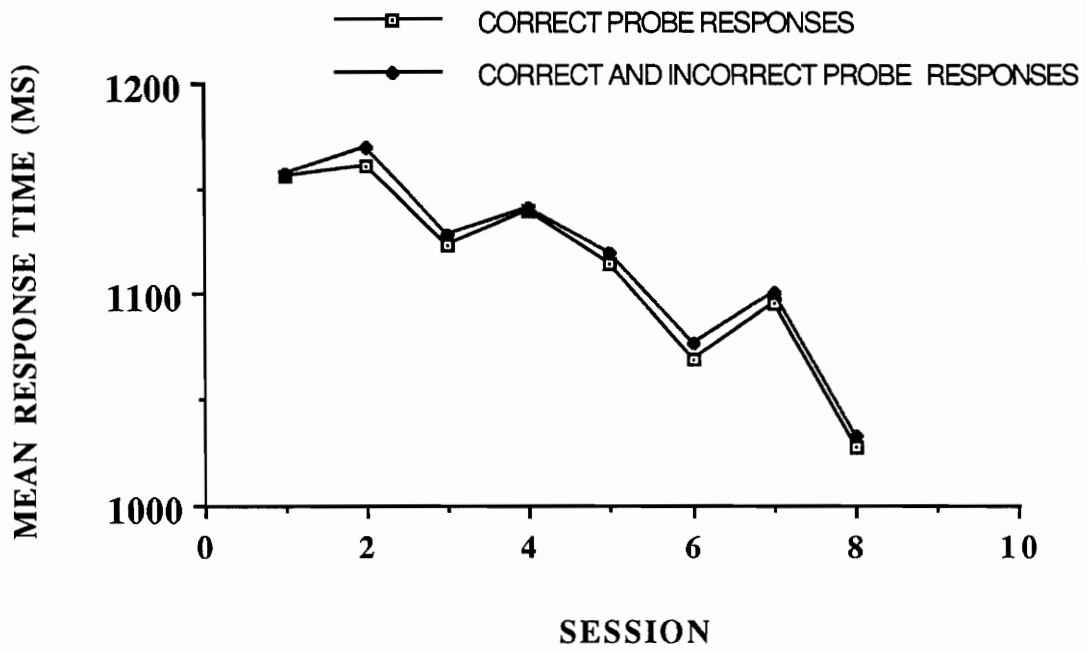


Figure 6. Sessions effect for mean response time to correct probe and both correct and incorrect probes.

TABLE 11

Newman-Keuls Comparisons for Session Effect for Mean Response Time (in ms) to the Correct Probe

Session	Time (ms)		
Session 2	1161.02	A	
Session 1	1156.46	A	
Session 4	1139.28	A	
Session 3	1123.54	A	B
Session 5	1113.87	A	B
Session 7	1095.17	A	B
Session 6	1069.75		B C
Session 8	1028.25		C

Means with the same letter are not significantly different, $p > 0.05$.

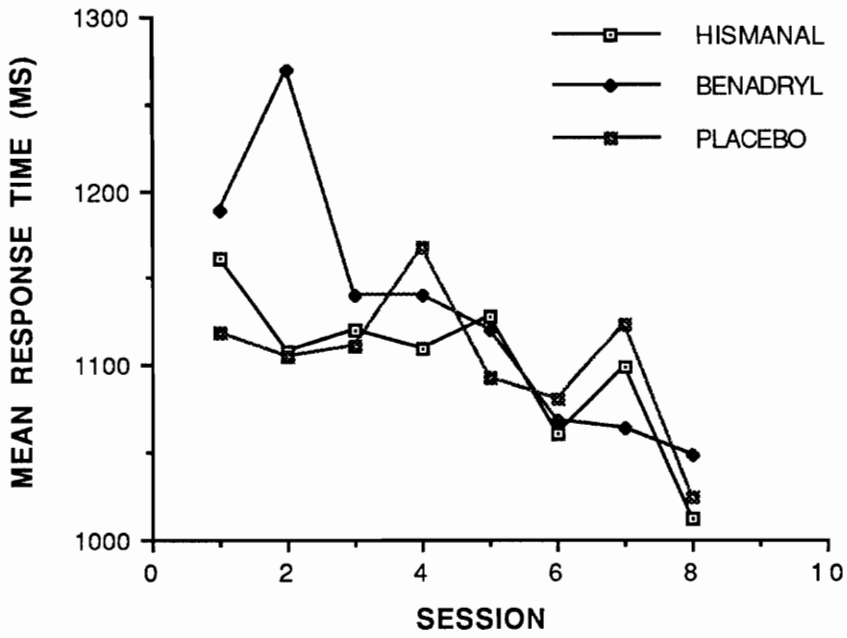


Figure 7. Session by drug interaction for mean response time to the correct probe.

TABLE 12

Simple-Effect F-tests of Sessions Across Drugs for Mean Response Time (in ms) to Correct Probe

Source of Variation	MS	F
Session 1	35730.25	1.93
Session 2	254144.70	13.76*
Session 3	6793.43	0.37
Session 4	24140.10	1.31
Session 5	9899.22	0.54
Session 6	2893.32	0.16
Session 7	26791.69	1.45
Session 8	9813.80	0.53

* $p < 0.05$

TABLE 13

Newman-Keuls Comparisons for Session 2 Drugs for Mean Response Time to Correct Probe

Drug	Time (ms)	
Benadryl	1269.1034	A
Hismanal	1108.5862	B
Placebo	1105.3793	B

Means with the same letter are not significantly different, $p > 0.05$.

TABLE 14

Analysis of Variance Summary Table for Mean Response Time (in ms)
to Both Probes

Source of Variation	df	MS	F	p
<u>Between Subjects</u>				
Subjects (Subj)	28	1833070.28		
<u>Within Subjects</u>				
Sessions	7	172995.66	6.56	0.0001
Sessions x Subj	196	26360.96		
Drug	2	68566.09	0.69	0.5057
Drug x Subj	56	99340.58		
Session x Drug	14	43744.66	2.46	0.0024
Session x Drug x Subj	392	17784.48		
Total	695	102140.77		

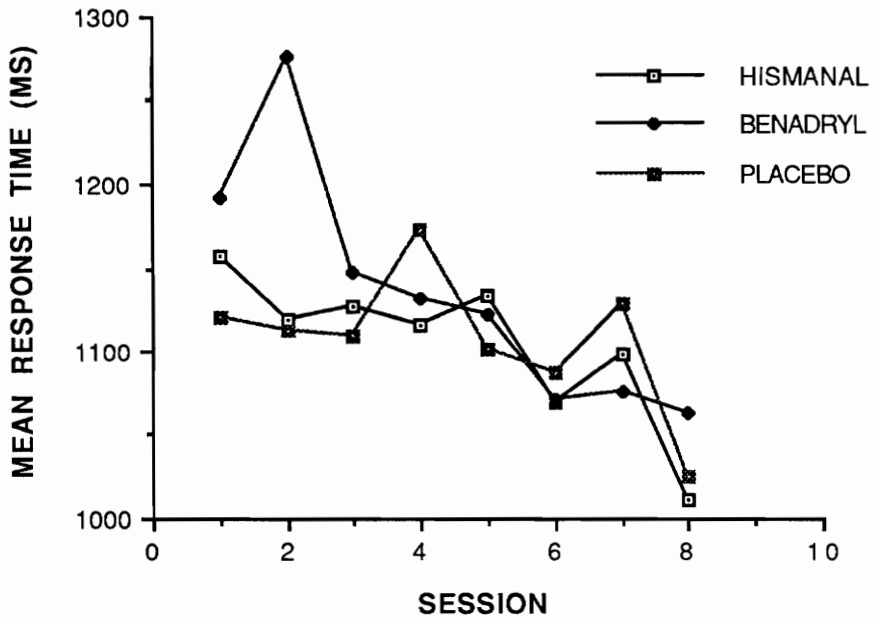


Figure 8. Session by drug interaction for mean response time to both probes.

TABLE 15

Newman-Keuls Comparisons for Session Effect for Mean Response Time to Both Probes

Session	Time (ms)			
Session 2	1169.41	A		
Session 1	1156.84	A		
Session 4	1140.67	A	B	
Session 3	1128.07	A	B	
Session 5	1119.00	A	B	
Session 7	1101.07	A	B	
Session 6	1076.28		B	C
Session 8	1033.32			C

Means with the same letter are not significantly different, $p > 0.05$.

TABLE 16

Simple-Effect F-tests for Sessions Across Drugs for Mean Response Time (in ms) to Both Probes

Source of Variation	MS	F
Session 1	37048.70	2.08
Session 2	251638.86	14.15*
Session 3	10329.93	0.58
Session 4	25213.32	1.42
Session 5	6910.59	0.39
Session 6	2879.41	0.16
Session 7	20340.66	1.14
Session 8	20417.25	1.15

* $p < 0.05$

TABLE 17

Newman-Keuls Comparisons for Session 2 Drugs for Mean Response Time to Both Probes

Drug	Time (ms)	
Benadryl	1276.9310	A
Hismanal	1118.3448	B
Placebo	1112.9655	B

Means with the same letter are not significantly different, $p > 0.05$.

TABLE 18

Analysis of Variance Summary Table for the RMS Tracking Error

Source of Variation	df	MS	F	p
<u>Between Subjects</u>				
Subjects (Subj)	28	2986.92		
<u>Within Subjects</u>				
Sessions	7	347.49	6.34	0.0001
Sessions x Subj	196	54.77		
Drug	2	120.72	0.42	0.6572
Drug x Subj	56	285.40		
Session x Drug	14	122.68	2.89	0.0004
Session x Drug x Subj	392	42.49		
Total	695	189.06		

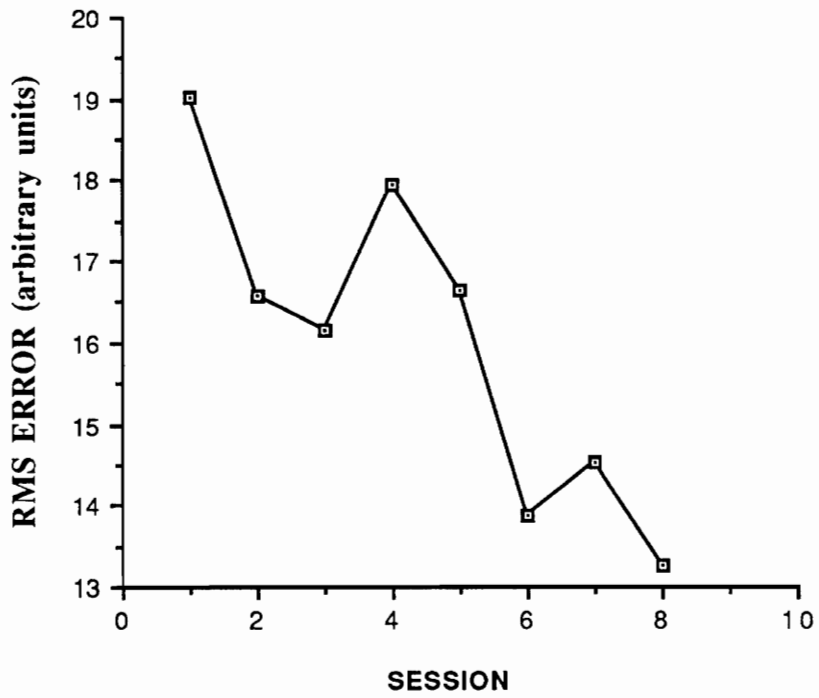


Figure 9. Sessions effect for the RMS tracking error.

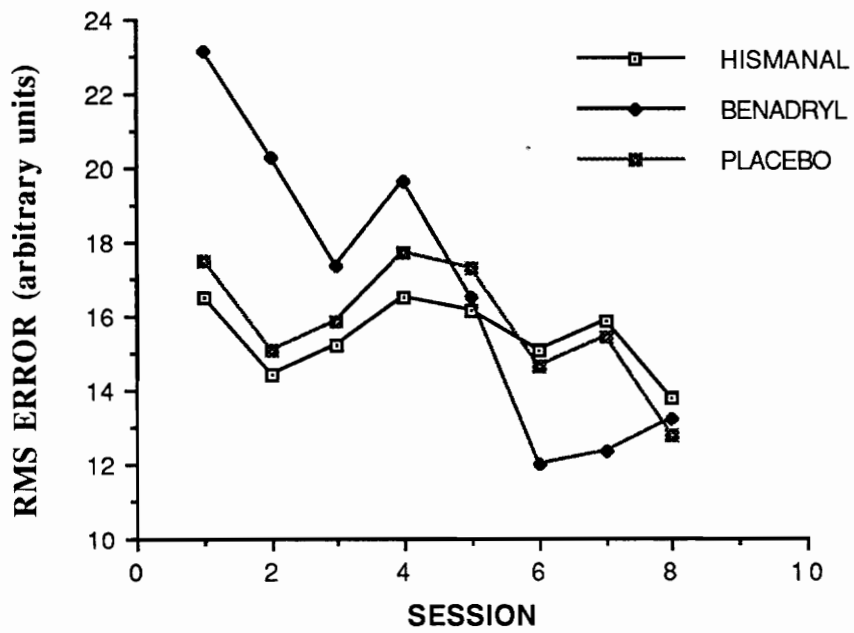


Figure 10. Session by drug interaction for the RMS tracking error.

TABLE 19

Newman-Keuls Comparisons for Session Effect of the RMS Tracking Error

Session	RMS Error (arbitrary units)			
Session 1	19.036	A		
Session 4	17.945	A		
Session 5	16.647	A	B	
Session 2	16.597	A	B	
Session 3	16.160	A	B	C
Session 7	14.534		B	C
Session 6	13.880		B	C
Session 8	13.257			C

Means with the same letter are not significantly different, $p > 0.05$.

TABLE 20

Simple-Effect F-tests for Sessions Across Drugs for the RMS Tracking Error

Source of Variation	MS	F
Session 1	370.87	8.73*
Session 2	302.21	7.11*
Session 3	34.93	0.82
Session 4	70.59	1.66
Session 5	10.35	0.24
Session 6	79.33	1.87
Session 7	104.15	2.45
Session 8	7.06	0.17

* $p < 0.05$

TABLE 21

Newman-Keuls Comparisons for Session 1 Drugs for RMS Tracking Error

Drug	RMS Error (arbitrary units)	
Benadryl	23.1241	A
Placebo	17.4931	B
Hismanal	16.4897	B

Means with the same letter are not significantly different, $p > 0.05$.

TABLE 22

Newman-Keuls Comparisons for Session 2 Drugs for RMS Tracking Error

Drug	RMS Error (arbitrary units)	
Benadryl	20.3034	A
Placebo	15.0828	B
Hismanal	14.4034	B

Means with the same letter are not significantly different, $p > 0.05$.

DISCUSSION AND CONCLUSIONS

General

The objective of this research was to determine whether a complex cognitive task showed a deterioration under the influence of two antihistamines (hismanal and benadryl) and to determine if the chosen task was of sufficient sensitivity to register decrements in performance at therapeutic dose levels of the two antihistamines. In the expected outcome, the hismanal antihistamine would produce no significant effects while benadryl would produce significant effects. This result would coincide with the expected lower incidence of central nervous system effects (Krstenansky and Cluxton, 1987) for hismanal and the expected central nervous system effects of benadryl (Cohen et al., 1984; Gengos and Gabos, 1987; Moskowitz and Burns, 1988).

Also, in the expected outcome, the hismanal group would not perform significantly different than the placebo. The mean response time to the incorrect probe showed the only drug effect and this was due to the benadryl group performing significantly slower than the placebo and hismanal groups (Table 9). For all the other dependent variables, the Newman-Keuls comparison test at session 2 (three hours after ingestion) shows benadryl to perform significantly poorer than the hismanal and placebo groups, which is in accordance with expected results.

Sessions

The presence of a session effect on all the dependent variables

was expected due to the known central nervous system effects of benadryl. For all the mean response times, a performance deterioration was expected for session 2 because of peak plasma concentrations appearing within one to four hours after ingestion of benadryl. All mean response times exhibited a deterioration in performance at this session. Tracking results were also expected to indicate a deterioration in performance at session 2 although this did not occur. Subjects' tracking performance improved by 13% over session 1. This may be due to practice effects occurring, which is surprising because subjects had been given training prior to the experiment to reduce such effects.

A deterioration in performance was also expected at session 4 and session 7 because these sessions followed the mid-day and night-time meals. All dependent variables except the mean response time to the incorrect probe manifested this expectation. This variable did not result in a performance degradation at session 4; instead, a nonsignificant 2% improvement occurred.

A look at the performance over sessions for each dependent variable reveals a general trend of improvement over the day. Practice effects were not expected but an improvement by the benadryl group due to a benadryl concentration decrease was expected. Also, the subjects utilized in this study were students, which may have presented an effect given most students' time schedules. Students tend to rise late and go to bed late. This could account for the improvement over the day.

Drugs

A significant drug main effect was produced only by the mean response time to the incorrect probe variable. Benadryl, as expected, was the cause of this significance. The performance of the hismanal group did not vary significantly from the placebo group.

Session by Drug Interaction

The significant interaction of session and drug was expected to occur. Benadryl was expected to peak at one to four hours after ingestion, which would cause a performance deterioration. In fact, this is what occurred for three of the four variables. The mean response time to the incorrect probe did not display a significant drug effect at session 2, but the sessions effect indicates session 2 to be significantly different from session 8. This difference may be construed as the result of the benadryl effect. The lack of a significant effect by hismanal in these interactions was also expected because of its lower incidence of central nervous system effects. In addition, the observation that hismanal did not differ significantly from the placebo leads to the conclusion that hismanal did indeed exhibit a lower incidence of central nervous system effects as measured by response time and tracking error.

The tracking portion of the task also indicated a significant result at session 1. This suggests the possibility of greater sensitivity inherent to the tracking task, which is in agreement with results found by White and Rumbold (1988). These significant results at session 1 and session 2 also concur with results found by Rice (1990) involving the unstable tracking task utilized in her dissertation work.

Conclusions

In drawing an overall conclusion, performance of the tracking/memory search task was significantly affected by benadryl while hismanal did not significantly affect performance. This conclusion is in agreement with Rice's (1990) research. The task is also concluded to be of sufficient sensitivity to register decrements in performance caused by antihistamines.

With respect to just the tracking portion of the task, it is noted that greater sensitivity to the effects of antihistamines is presumed when compared to the memory search portion of the task (White and Rumbold, 1988). This is due to the facts that tracking tasks are oriented toward response execution in information processing terms (Perez et al., 1987) and that antihistamines are associated with the side effect of disturbed coordination (ASHP, 1988). With respect to the memory search portion of the task, antihistamines are known to affect reaction time (Cohen et al., 1984; Cohen et al., 1987; Gengo and Gabos, 1987) which is also supported by this study.

Future Research

Given the benefit of hindsight, there are a number of suggestions with regard to future research which might be of some value, as follows:

1. As stated earlier, the mean half-life of hismanal ranges from 9.2 to 13 days with single doses and 18 to 20 days after two weeks to five months of usage (Krstenansky and Cluxton, 1987). Also, the median time to onset of action is 48 hours (Richards et al., 1984). This suggests that hismanal has a long duration of action and that it is metabolized slowly. This knowledge leads to the suggestion of an extended study being conducted over weeks or months in order to fully appreciate the effects of hismanal under more typical usage conditions.

2. Hismanal does not cross the blood-brain barrier easily and has a higher affinity for lung histamine-receptors than cerebellar histamine-receptors, which is one possible explanation for the lower incidence of central nervous system effects (Krstenansky and Cluxton, 1987). These characteristics place hismanal in a different class of antihistamine when compared to benadryl, which is known to cross the blood-brain barrier with ease. Because of this, it is suggested that hismanal be tested with other antihistamines of the

same nature in order to further generalize the results.

3. This study was conducted with only males because of the necessity for pregnancy screenings prior to each test session if females were to be used. Another study utilizing females would also enable greater generalization of results.

4. Finally, the use of students as the subject population may have influenced the results because of the lifestyle of such students. Therefore, it is suggested to expand the subject population to include people of different ages and occupations.

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APPENDIX

**Complex Cognitive Performance and Antihistamine Use
Consent Form Information Page**

Virginia Polytechnic Institute and State University (VPI&SU)
Industrial Engineering and Operations Research Department
Human Factors Engineering Center
Whittemore Hall

The purpose of this research is to examine the effects of antihistamines on cognitive performance, visual-motor skills, and mood. Antihistamines can be purchased at drug stores and are typically used for relief of cold or allergy symptoms. This research is important to discern what types of jobs can be done safely and effectively while taking antihistamines. In this experiment you will be trained on four computerized tests until your performance is at an even level. Training will take approximately 10 to 15 hours. The actual amount of time will vary for each individual. Four training sessions will be scheduled, each one for 3 hours. The tests will record your ability to do things such as planning, problem solving, and making decisions. A fifth test will evaluate your visual-motor coordination. You will also be asked to answer questions about how you feel, how you think you did on the tests, and which antihistamine you think you were given. The data collected will be treated with anonymity.

After reaching an even level of performance, you will be scheduled for three testing sessions one week apart. Each session will start at 7:00 am and will last until 11:00 pm. At 7:00 am, you will be given either a placebo or an antihistamine tablet. The placebo has no active ingredients. You will be tested, using the tests described above at 8:00 am, 10:00 am, 12:00 pm, 2:00 pm, 4:00 pm, 6:00 pm,

8:00 pm, and 10:00 pm. You will be permitted to read, study, talk, or watch television between testing. Test sessions will be in the Human Factors Engineering Center, 5th floor, Whittemore Hall, VPISU.

Your medical records and a questionnaire will be reviewed by a licensed physician prior to being accepted for participation. You will not be allowed to participate if you have experienced adverse reactions to antihistamines, if you are currently taking prescribed or over-the-counter medications, if evidence of adverse medical conditions as judged by a physician are found, if you smoke, if you do not agree to refrain from caffeine consumption during test sessions, or if you have less than 20-20 corrected vision.

The antihistamines are being given to you at the same level that you would normally take them if you had a cold or had hay fever. They should not be harmful, but may make you feel drowsy or sluggish. Should difficulties occur during the experiment, a licensed physician will be on call at all times. You will not be allowed to participate if you have never used an antihistamine previously.

The research team includes:

1. Dr. H. L. Snyder, Faculty Member, IEOR Dept.
2. Valerie J. Berg Rice, Graduate Student, IEOR Dept.
3. Phillip Barkley, M. D., Medical Director, VPI&SU
Health Services
4. Charlotte Waggoner, Graduate Student, IEOR Dept.
5. Gail Whitehouse, Graduate Student, IEOR Dept.

INFORMED CONSENT

1. You are being asked to volunteer to be a subject in a research project whose purpose and description are contained in the document "Complex Cognitive Performance and Antihistamine Use," which you have already read.

2. There are some risks and discomforts to which you expose yourself in volunteering for this research.

The risks are:

- a. Adverse side effects may be experienced as a result of antihistamine use. The most common side effects that are reported include sedation, sleepiness, dizziness, disturbed coordination, and drying effects such as dry mouth. If you do experience side effects, they should all be gone by the end of the testing session.
- b. Other side effects which are reported less often, but which are noted on a typical "over-the-counter" preparation of an antihistamine are listed below. (Indications for use, contraindications, warnings, and precautions which are noted on over-the-counter preparations will be provided on request.) Please inform the investigators if you experience any of the side effects noted below.
 1. General: urticaria (hives), rash, anaphylactic shock (ineffective circulation due to hypersensitivity to specific substances), sensitivity to light (photosensitivity), excessive perspiration, chills, dryness of mouth, nose, and throat.
 2. Cardiovascular system: hypotension, headache, palpitations, fast heart beat (tachycardia), irregular heart beat (extrasystoles).
 3. Hematologic system: hemolytic anemia (reduction of the number of red corpuscles), thrombocytopenia (persistent decrease in the number of blood platelets),

agranulocytosis (absence of granulocytes from the circulating blood).

4. Nervous system: sedation, sleepiness, dizziness, disturbed coordination, fatigue, confusion, restlessness, excitation, nervousness, tremor, irritability, insomnia, euphoria, paresthesia (a sensation of pricking, tingling, or creeping on the skin with no objective cause), blurred vision, diplopia (double vision), vertigo, tinnitus (a sensation of "ringing" in the ears), acute labyrinthitis (inflammation of the inner ear), neuritis, convulsions.
 5. GI system: stomach discomfort (epigastric distress), lack of appetite (anorexia), nausea, vomiting, diarrhea, constipation.
 6. GU system: urinary frequency, difficult urination, urinary retention, early menses.
 7. Respiratory system: thickening of bronchial secretions, tightness of the chest and wheezing, nasal stuffiness.
- c. A member of the research team will ask you if you understand the above terms and explain any of them to you, should you not understand them.
 - d. Both antihistamines that will be used have Federal Drug Administration (FDA) approval.

The following precautions will be taken:

- a. Your medical records and a questionnaire that you will fill out will be screened by a licensed physician.
- b. You will not be allowed to participate if you have experienced adverse reactions to antihistamines, if you are currently taking prescribed or over-the-counter medications, if evidence of adverse medical conditions as judged by a physician are found, if you smoke, if you do not agree to abstain from caffeine consumption during the study, or if you have less than 20-20 corrected vision.

- c. You will not be allowed to participate if you have never used an antihistamine previously.
- d. Should difficulties occur during the experiment, a physician will be on call at all times.
- e. A member of the research team will be present and available throughout the experimental sessions.
- f. Your heart rate will be monitored during the test sessions.
- g. The principal investigator should be contacted regarding any research related injuries. The principal investigator is Dr. H. L. Snyder. His office is in room 547 Whittemore Hall, VPISU, 231-7527.

The potential discomforts in this experiment are;

- a. The total length of the training sessions until you reach a level performance. Each training session will be scheduled for three hours. It is expected that the total amount of time for training will take from 10 to 15 hours. The total amount of time may vary for each individual.
- b. The length of the three experimental sessions, each of which will last 16 hours. Testing will occur every two hours and you will be permitted to sleep, study and rest in between testing.
- c. The total estimated time requirement for participation in this study is 60 hours (10-15 hours of training and 3 testing sessions of 16 hours each). It is extremely important that you seriously consider your professional and/or academic requirements prior to agreeing to the time commitment required in this study.

3. The data gathered in this experiment will be treated with anonymity. Shortly after you have participated, your name will be separated from your data.

4. While there are no direct benefits to you from this research (other than payment), you may find the tasks interesting.

Your participation, along with that of the other volunteers, should make it possible to discover what types of mental and physical skills are affected by antihistamine use. It will also help to determine when or if antihistamines can be safely used by military and civilian pilots (or other persons operating critical machinery).

5. You should not volunteer for participation in this research if you are under 18 years old, if you are not in good health, if you are not male, if you smoke or use tobacco products, or if you have taken any drug, alcoholic beverage, or medication for 24 hours prior to and following test sessions. It is your responsibility to inform the experimenters of any additional condition which might interfere with your abilities. Such conditions would include inadequate sleep, hunger, hangover, headache, cold symptoms, depression, allergies, emotional upsets, visual impairment, seizures (fits), nerve or muscle disease, or other similar conditions.

6. You will be required to refrain from caffeine consumption throughout each day of the study.

7. The principal investigator, Dr. H. L. Snyder, of the research project and his associates will answer any questions that you may have about this project. You should not sign this consent form until you are satisfied that you understand all of the previous descriptions and conditions.

8. You should further be aware that you may contact Dr. Stout, Chairman of the University's Institutional Review Board, 339 Burruss Hall, VPISU, if you have questions or concerns about this experiment. His phone number is (703) 231-5281.

9. You should know that at any time you are free to withdraw from participation in this research program without penalty. If you should decide to withdraw while an experimental session is being run, you will be required to stay until the end of that session. This is for your protection, should you experience negative effects from the antihistamine.

If you decide to participate, you will be paid \$4.00 per hour for the time that you actually spend. If you complete the entire experiment, you will be paid \$5.00 per hour. Payment will be made shortly after you have finished your participation. You will not receive or become entitled to any compensation other than that mentioned.

10. You will receive a copy of this consent form.

11. The possibility exists that representatives of the United States Army Medical Research and Development Command may inspect the records of this research study, although your name will not be contained in those records.

12. Signature of the volunteer and date:

I have read and understand the scope of this research project and I have no other questions. I hereby give my consent to participate. I understand that I may stop participation if I choose to do so, however; I realize that once a testing session has begun, I will be required to remain for the entire testing session.

Signature (printed)_____

Signature (written)_____

Date_____

Subject's permanent address

13. Signature of a member of the research team and date:

Signature (printed)_____

Signature (written)_____

Date_____

14. Signature of witness, not a member of research team and date:

Signature (printed)_____

Signature (written)_____

Date_____

Additional Information (furnished on request)

Indications and Usage

1. antihistaminic: for allergic symptoms and conditions.
2. motion sickness: for active and prophylactic treatment of motion sickness.
3. antiparkinsonism: for adjunct treatment of parkinsonism.
4. nighttime sleep-aid.

Contraindications

1. use in the newborn or premature infant.
2. use in nursing mothers.
3. hypersensitivity to antihistamines of similar chemical structure.

Warnings:

Antihistamines should be used with considerable caution in patients/subjects with narrow-angle glaucoma, stenosing peptic ulcer, pyloroduodenal obstruction, symptomatic prostatic hypertrophy, or bladder-neck obstruction. In infants and children, especially, antihistamines in overdose may cause hallucinations, convulsions, or death. As in adults, antihistamines may diminish mental alertness in children. In the young child, they may produce excitation. Antihistamines are more likely to cause dizziness, sedation and hypotension in elderly patients.

Precautions:

1. General: atropine like action and should be used with caution in patients/subjects with a history of bronchial asthma, increased intraocular pressure, hyperthyroidism, cardiovascular disease or hypertension.
2. Information for patients/subjects: this drug may cause drowsiness and has an additive effect with alcohol. They should be

warned about engaging in activities requiring mental alertness such as driving a car or operating appliances, machinery, etc.

3. Drug interactions: has additive effects with alcohol and other central nervous system depressants (hypnotics, sedatives, tranquilizers, etc). Monoamine oxidase inhibitors prolong and intensify the anticholinergic (drying) effects of antihistamines.

4. Carcinogenesis, mutagenesis, impairment of fertility: Long term studies in animals to determine mutagenic and carcinogenic potential have not been performed.

5. Pregnancy: Reproduction studies have been performed in rats and rabbits at doses up to 5 times the human dose and have revealed no harm to the fetus. There are, however, no adequate and well controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Adverse reactions:

1. General: urticaria (hives), rash, anaphylactic shock, photosensitivity, excessive perspiration, chills, dryness of mouth, nose, and throat.

2. Cardiovascular: hypotension, headache, palpitations, tachycardia, extrasystoles.

3. Hematologic system: hemolytic anemia, thrombocytopenia, agranulocytosis.

4. Nervous system: sedation*, sleepiness*, dizziness*, disturbed coordination*, fatigue, confusion, restlessness, excitation, nervousness, tremor, irritability, insomnia, euphoria, paresthesia, blurred vision, diplopia, vertigo, tinnitus, acute labyrinthitis, neuritis, convulsions.

5. GI system: epigastric distress, anorexia, nausea, vomiting, diarrhea, constipation.

6. GU system: urinary frequency, difficult urination, urinary retention, early menses.

7. Respiratory system: thickening of bronchial secretions*, tightness of the chest and wheezing, nasal stuffiness.

*the most frequently reported adverse reactions.

VITA

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